Forum

Controversy and Quality Improvement: Lingering Questions About Ethics, Oversight, and Patient Safety Research

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A collaborative project between Johns Hopkins quality improvement (QI) and patient safety experts and the Michigan Health & Hospital Association (MHA)'s Keystone Center for Patient Safety and Quality evaluated the use of a safety program and checklist to reduce the rate of central line–associated bloodstream infections (CLABSI) in 103 intensive care units (ICUs) in Michigan. Results published in the *New England Journal of Medicine* documented a dramatic reduction in the rate of infections.[1] The project subsequently prompted a flurry of questions related to whether evaluating the patient safety intervention constituted human subjects research and, if so, whether any additional protections were necessary for the patients or clinicians involved. This article summarizes the project and discusses six ethical and regulatory issues relevant not only to this case but, more broadly, to evidence-based patient safety initiatives.

The Johns Hopkins–Michigan Study

CLABSI are a major source of morbidity and mortality in hospitals. These infections can prolong hospital stays and can result in significant additional hospital costs. In the United States alone, there are an estimated 80,000 catheter-related bloodstream infections each year, resulting in up to 28,000 deaths annually among patients in intensive care units (ICUs). The average cost of care for a patient with this type of infection is $45,000, with an estimated total cost of $2.3 billion annually for caring for persons with catheter-borne infections.[1]

The MHA's Keystone Center for Patient Safety & Quality was created in March 2003 as a 501(c)(3) division of the MHA Health Foundation to bring together experts, best practices, and data to improve safety at the bedside. The Keystone ICU initiative, in which MHA collaborates with Johns Hopkins University (JHU) patient safety experts, is one of several initiatives to improve the quality of care in Michigan hospitals.

In September 2003, the Agency for Healthcare Research and Quality (AHRQ), a federal agency that supports the study of evidence-based improvements in health service delivery and quality, awarded a grant to Johns Hopkins to evaluate, in collaboration with the MHA Keystone Center, an evidence-based safety initiative in Michigan ICUs. The initiative included an ICU–based safety program to improve the "culture of safety" and the use of a checklist to ensure that the following five evidence-based procedures for improving safety were followed during catheter insertion:

1. Hand-washing
2. Using full-barrier precautions
3. Cleaning the skin with chlorhexidine before insertion
4. Avoiding the femoral site if possible
5. Removing unnecessary catheters as soon as possible

For hospitals to be included, commitment from hospital leadership was required, and ICUs had to designate a physician and nurse team leader. ICU clinical leaders were given evidence supporting the use of these procedures and were asked to disseminate information to ICU colleagues. Teams were also given tools to improve teamwork and were encouraged to participate in monthly conference calls to review project content, to discuss challenges and successes with implementation, and to bring forward any questions that emerged from their local project-related efforts. Teams were told they would receive monthly feedback on number and rates of infections in their units and how their rates compared with aggregate data from other ICUs.

There was no randomization to intervention or control. All ICUs received the intervention, and measurement was conducted as a pre-post test design. Implementation of the intervention took approximately three months in each participating unit. A trained hospital-based infection control practitioner in each hospital, independent of the ICU staff implementing the intervention, collected monthly data on the number of catheter-related bloodstream infections in each unit and number of catheter days. Most, but not all, participating hospitals already were collecting these data, although the project ensured hospitals all used the Centers for Disease Control and Prevention (CDC) standard definition of CLABSI. Further, all

participating ICUs were asked to report the number of catheter days per month; this formed the denominator for calculating infection rates. Monthly, de-identified data were provided to the MHA Keystone Center, which created a data set; data aggregated to the ICU level were sent to Johns Hopkins for analysis. Follow-up data were collected monthly for 18 months.

The project was submitted to the Johns Hopkins Medical Institutions (JHMI) Institutional Review Board (IRB), which categorized it as "exempt" research under exemption category 4 because data provided to Johns Hopkins researchers were de-identified and the research represented minimal risk.[2] The exempt classification implies that individual, written informed consent is not required by federal regulations.

Data were reported beginning in March 2004 from 103 ICUs in 67 hospitals. Three months after the intervention was implemented, the median rate of catheter-related infections per 1,000 catheter days decreased from 2.7 infections at baseline to zero. The median rate of zero infections was sustained for the remaining 15 months of follow-up. The mean rate of catheter-related infections per 1,000 catheter days decreased from 7.7 infections at baseline to 1.4 infections at the end of follow-up.[1]

Regulatory Complaint

After these results were published, an anonymous complaint was filed with the federal Office for Human Research Protections (OHRP).[3] The complaint questioned whether it was appropriate to classify the activity as exempt research, whether every participating Michigan hospital should have had a federalwide assurance (FWA; a contract between the institution and OHRP, assuring that federally funded human subjects research from the institution will be reviewed by a properly constituted IRB); whether IRB review should have occurred at each participating Michigan hospital, and whether individual informed consent should have been obtained from patients and clinicians at participating Michigan hospitals. Ultimately, OHRP made the determination that (1) the Johns Hopkins IRB was incorrect in classifying the research as exempt; (2) as such, Michigan hospitals participating in this federally funded activity should each have had an FWA; (3) Michigan hospitals should each have had an IRB review the activities; and (4) "JHU failed to ensure that the requirements for obtaining and documenting the legally effective informed consent of the subjects…was satisfied. OHRP notes that the subjects of the research were both the healthcare providers at the participating ICUs and their patients."[4]

Ethical and Regulatory Issues

1. Was This Project Human Subjects Research? Was It QI? And Does That Distinction Matter?

A key question raised by this project, and germane to all QI initiatives with rigorous evaluation, is whether the entire activity, or certain pieces, constitute human subjects* research. This project measured the effectiveness of systemwide changes and a checklist to improve "the culture of safety" and to encourage physicians to follow five evidence-based practices when inserting venous catheters. Many QI projects evaluate if system changes, such as putting up signs, double-checking orders, providing reminders, or having needed supplies more conveniently available can improve adherence to practices already known to be associated with high-quality care. Thus, if a system to remind physicians to implement care they should arguably be providing anyway is evaluated, which pieces, if any, involve human subjects research?

Operationally, the answer determines whether, under current federal regulations, the activity must be reviewed by an IRB. Ethically, the distinction is relevant as well. Hospitals collect—indeed are required by regulators, accreditors, and insurers to collect—quality assurance data as one means of making certain the care delivered to patients is of consistently high quality. In hospitals, it is generally understood that records periodically will be reviewed to ensure that the care patients receive is maintained at the highest standard. Research, however, is designed to learn new things about what works and to generate knowledge that is more broadly applicable. When research involves human subjects, any intrusion on their interests or rights must be justified by an assessment that these intrusions are ethically acceptable, and, in most but not all circumstances, the express consent of the subjects must be obtained.

Systematic studies of the effects of patient safety interventions frequently involve a combination of research methods, some but not all of which involve human subjects. Moreover, when patient safety research involves human subjects, the risks to them can be minimal and the specifics of the projects, particularly when the intervention is to be implemented in ways that make it impossible to disentangle from medical care, may

* The federal regulations define human subject as a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information (Department of Health & Human Services Protection of Human Subjects, 45 C.F.R. 46.102(f), 2005). Of note, OHRP also provides guidance on when an activity is not human subjects research subject to federal oversight. This states that prospective collection of de-identified data is not considered human subjects research subject to federal oversight (Office for Human Research Protections: *Human Subject Regulations Decision Charts*. Sep. 24, 2004. http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm (last accessed Apr. 15, 2008).

limit the meaningfulness of consent in term of decision making, even if it were obtained.

Although some scholars have suggested strategies to distinguish research from nonresearch initiatives or have suggested that QI activities be reviewed as research absent other systems of ethical oversight,[5–8] these proposals differ in important ways and have not yet found their way into regulation or guidance statements. Indeed, from a regulatory standpoint, in identifying what does or does not constitute human subjects research subject to federal regulation, it is the opinion of OHRP that counts. In the current climate of regulatory uncertainty, however, a moral hazard of this uncertainty is that fewer formal patient safety studies may be undertaken, resulting in a slowdown in progress in patient safety. For example, several states that were considering replicating the Michigan project have raised concerns about proceeding because of the issues raised by OHRP.

Unlike the development of new pharmaceuticals, which cannot by law proceed to market until evidence of their safety and efficacy is established through rigorous human subjects research, new approaches to patient safety have no similar legal mandate. To the extent that patient safety experts or hospital leadership anticipate that evaluation and dissemination of their innovative ideas will encounter regulatory landmines, fewer formal safety studies may be conducted. Research has demonstrated life-saving benefits from such innovative practices as repeating verbal orders, standardizing dosing abbreviations, and creating computerized reminder systems. Such innovation is essential and clearly is associated with fewer problems for patients and with fewer deaths. To ensure that such innovation can continue, however, thoughtful discussion is needed about the nature and types of oversight appropriate for this type of work and the subsequent promulgation of clear regulatory guidance.

2. When Is Patient Safety Research Exempt, Expedited, or Greater than Minimal Risk, and Does the Current Regulatory System Work for QI Research?

The Johns Hopkins IRB classified the JHU–Michigan patient initiative as "exempt," using category 4, because Johns Hopkins was receiving only de-identified data:

> *Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.*[2]

In its exchange with Johns Hopkins, OHRP made clear that this exemption category applies only to de-identified (or publicly available) data that existed *before* the IRB submission. Research entailing the *prospective* collection of data, according to this exchange, cannot be categorized as exempt; instead, it can be classified as "expedited" if it involves minimal risk. Indeed, a recent statement by OHRP suggests that, in retrospect, an expedited review of the JHU–Michigan patient safety study would have been appropriate.[9] For investigators of other minimal risk safety initiatives that also seek to collect prospective data to evaluate an intervention, an expedited review may be considered suitable.[10]

Some scholars question whether the existing human subjects oversight mechanism, designed largely with medical research in mind, is an appropriate model for QI research.[5,6] Considering the development of a completely separate review and oversight mechanism would raise questions about what other types of human subjects research (public health practice research, qualitative behavioral research) would also benefit from an alternate system. From a practical perspective, it may be more sensible to identify the arenas where current regulations are an awkward fit and try to address those specifically. Whether an additional exemption category is needed, whether (as described below) more readily available mechanisms for centralized review can be adopted, and whether guidance describing when systems research counts as human subjects research may be areas for exploration.

Whatever mechanism is selected, it is important that it not provide a disincentive to conducting robust evaluations of patient safety initiatives. OHRP stated that hospitals can use the checklist as long as they do not measure its impact, for if they did, such activities would be research subject to federal regulations.[11] Such a statement raises concern. As stated earlier, such a view encourages healthcare organizations to implement safety initiatives viewed simply as "good ideas" without then "measuring their impact," because the latter would be subject to the burdens of review and oversight. Yet, it is in the public's interest to have patient safety activities vetted and evaluated; indeed, the public should have confidence that inferences regarding the quality of care provided by health care organizations are valid and reliable.[12]

3. Is IRB Review Necessary at Every Site Where Data Are Collected?

For projects that are viewed and labeled as human subjects research, a relevant operational question becomes whether IRB review is appropriate and necessary at every participating insti-

tution. The Johns Hopkins–Michigan patient safety project as reported in the *New England Journal of Medicine*, for example, involved 67 different hospitals, of which 30 (45%) did not have an IRB. The OHRP determination letter to Johns Hopkins stated that an FWA and local IRB review should have been in place at *each* participating hospital.[4]

For large, multisite patient safety studies, it may be important, however, to identify alternative mechanisms that honor the critical goals of patient protection and local acceptability while not unduly compromising the evaluation from moving forward or the participation of many local sites. After the Michigan study was published, for example, Johns Hopkins investigators were approached by another state to implement this same safety intervention in hospitals in their state and again measure infection rates. This second state's rural hospitals, however, are less likely than those in urban areas to have IRBs and also are less likely to have previously participated in sophisticated patient safety initiatives. It would be unfortunate if rural or small hospitals were systematically excluded from such evaluations for lack of IRBs.

Various research groups and/or commentators have proposed and/or implemented centralized IRB review mechanisms for analogous situations in an attempt to address both the need for high-quality ethics review and the need to streamline a process that otherwise could potentially involve dozens or even hundreds of different committees.[13–16] Although such creative solutions occasionally have been achieved, a centralized approach is not a readily available regulatory option for many researchers. Again, perhaps additional regulatory language that lays out the circumstances and conditions under which a centralized approach could be used would be valuable.

For future patient safety research projects with Michigan hospitals, it is likely that the MHA Keystone Center will apply for an FWA that would cover all Michigan hospitals. Having the MHA Keystone Center take on this role makes logical sense, given its mission of furthering the quality of care in Michigan hospitals. Moreover, the MHA Keystone Foundation is more directly involved in the *evaluation component* of patient safety activities than are local hospitals, and thus it is more appropriate that it (rather than the hospitals) be responsible for obtaining an FWA and maintaining an IRB. Obviously, the existence of centralized oversight never precludes a local hospital from deciding to require its own review. Rather, it allows smaller hospitals and organizations who do not have the infrastructure but who support and want to be part of evidence-based QIs to be included.

4. Is Informed Consent Necessary?

If a research activity poses no more than minimal risk to human subjects, then federal regulations allow investigators to request a waiver of the requirement to obtain informed consent. Federal regulations also state that, for this waiver to be granted, investigators must demonstrate that it will not adversely affect the rights and welfare of subjects and that the research could not practicably be carried out without the waiver.[17]

In the Michigan patient safety study, participating ICUs implemented the intervention with the intent that it be adopted by all ICU staff and applied to all relevant patients. As such, there was no meaningful way for patients or staff to refuse to participate in the intervention. By contrast, patients could have refused permission to have their de-identified data included in the study. Arguably, however, soliciting consent for this purpose is of limited ethical value from the standpoint of the interests of patients and would have imposed such a significant administrative burden on the project as to make the research infeasible.

5. Should Funding Be Relevant?

In its most recent determination letter to Johns Hopkins, OHRP acknowledged that funding from AHRQ was no longer being used and "that no federal funds, directly or indirectly, support JHU's continuing collection of data from the Michigan hospitals."[11] What makes a project research rather than exclusively quality assurance, however, is not who funds it but, rather, the project's intentions and goals. Most research institutions (including Johns Hopkins) have FWAs that require all human research to be reviewed, regardless of funding. Ethically, human beings deserve proper protection, and who funds the activity is irrelevant to this moral mandate.

6. How Much Evidence Is Sufficient Before Research Interventions Should Be Recommended as Standard of Care?

After the Johns Hopkins–Michigan study was published, OHRP stated that the checklist, as used in Michigan, could now be considered standard care, and thus Michigan hospitals did not need to obtain IRB review for using the checklist or for collecting data from that point forward.[11] A critical ethical question for many types of research, not just research into QI, is what constitutes sufficient empirical evidence that a new intervention is worthy to be recommended as standard practice?[18] Clearly, a variety of considerations are relevant, including how many studies were conducted, what types of studies were conducted, how rigorous the design was, how burdensome or costly the intervention is, and the magnitude and nature of the

benefits identified. Although there is intuitive appeal to assuming that a study with findings as dramatic as the Johns Hopkins–Michigan study will uniformly be "true," this remains an empirical question. Ethically, it is important to consider whether additional studies in other locations and other types of hospitals also should be conducted, as well as whether new safety practices are followed and reduced rates of infections are sustained over time. Operationally, whether such future studies ought to be considered human subjects research (and subject to IRB review) or not, particularly in light of OHRP's recent determination, is important to resolve.

Conclusion

Patient safety research has identified multiple mechanisms that improve outcomes, reduce deaths, and lower costs. It is only after systematic evaluation, using rigorous definitions and designs, however, that new ideas actually *ought* to be implemented widely. Perhaps a benefit of the publicity given to the Johns Hopkins–Michigan study will be (1) better understanding that research of this sort is important, (2) better clarity on how to classify this research, and (3) creative regulatory solutions for streamlining oversight in ways that ensure patients are protected, both during safety studies and by having better evidence to guide their care in the future. We look forward to continued dialogue with OHRP, consumers, researchers, ethicists, clinicians, health care organizations, policy makers, employers, and insurers to address the questions addressed in this article and thereby to help mature the science of patient safety and QI. J

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